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EDITORIAL

Age related changes in pancreatic beta cells: A putative extra-cerebral site of Alzheimer's pathology

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Abstract

Frequent concomitant manifestation of type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) has been recently demonstrated by epidemiological studies. This might be due to functional similarities between β-cells and neurons, such as secretion on demand of highly specific molecules in a tightly controlled fashion. An additional similarity represents the age-related alteration of hyperphosphorylated tau in AD patients. Similarly, alterations have been identified in β-cells of T2DM patients. The islet amyloid polypeptide has been associated with β-cell apoptosis. As a consequence of increasing age, the accumulation of highly modified proteins together with decreased regenerative potential might lead to increasing rates of apoptosis. Moreover, reduction of β-cell replication capabilities results in reduction of β-cell mass in mammals, simultaneously with impaired glucose tolerance. The new challenge is to learn much more about age-related protein modifications. This can lead to new treatment strategies for reducing the incidence of T2DM and AD.

Key words: Type 2 diabetes mellitus; Pancreatic beta cells; Age; Alzheimer's disease; Hyperphosphorylated tau; Islet amyloid polypeptide

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INTRODUCTION

Prevalence of impaired glucose tolerance and type 2 diabetes mellitus (T2DM) is increasing among the elderly in humans. The absolute number of T2DM patients is rising worldwide, particularly in industrialized countries. This is not only because of the higher incidence of obesity and reduced physical exercise, but is also due to the longer life expectancy in these countries, as well as superior food quality, and the availability of highly effective medication. However, a longer life span brings with it age-associated

diseases such as diabetes mellitus type 2, cognitive disorders, and Alzheimer's disease (AD). Primarily, one would not expect that these two very different forms of age related complications (TD2M and AD) to have any connection. Yet, epidemiological studies have demonstrated that, when compared with age matched individuals with absence of cognitive dysfunction[1,2] , impaired glucose tolerance and T2DM is more prevalent among AD patients. The link between these entities with different loci of pathological processes might be found in similar key mediators or signaling pathways. In both, the pancreatic beta cell and neurons of the central nervous system, secretion on demand of highly specific molecules represents a genuine task. This is mediated *via* a tightly controlled exocytosis process. The SNARE (soluble N-ethylmaleimide-sensitive-factor attachment protein receptor) protein complex gears transmitter and insulin secretion at neurons and beta cells, respectively. The SNARE complex exerts its function at the neuronal synapse and in the β-cell, using already pre-primed mature granules. Three so called SNARE proteins participate in fusing the vesicles to the plasma membrane: the vesicle-associated membrane protein (VAMP, also called synaptobrevin); syntaxin, an integral plasma membrane protein; and the synaptosomal-associated protein of 25 kDa (SNAP-25), anchored to the plasma membrane *via* a palmitoyl group. Together, these three proteins form a helical bundle consisting of four amphipathic helices, or SNARE motifs, two of which are contributed by SNAP-25[3]. It is believed that assembly of the SNARE complex proceeds in a zipper-like fashion from the N-terminal end of the interacting helices toward the C-terminal membrane anchors. In this way, assembly of the proteins in the opposing membranes pulls the membranes together[4]. At the beginning of membrane fusion, the SNARE proteins are located in still separated membranes (so-called *trans*-complexes) and, after fusion, the trans-membrane segments of the SNAREs are present in the same membrane (*cis*-complexes). To restore the cell for new exocytosis events, the *cis*-complexes are then disassembled by NSF (N-ethylmaleimide-sensitive factor) and additional cofactors[5], and vesicles containing VAMP are recycled. Secretagogin, a novel hexa EF-hand calcium-binding protein was recently found to interact with SNAP-25[6]. Further complex interdependencies will be demonstrated in establishing inter-actoms[7].

ALZHEIMER'S PATHOLOGY IN PANCREATIC β-CELLS

As most cellular processes are regulated by multi-protein complexes, abolishing or enhancing a protein-protein interaction may have a profound impact and possibly manifests in distinct diseases. Since protein-protein interactions are critical events for a wide range of physiological and pathological processes, the precise control of these interactions and their biological consequences present a major challenge and opportunity for modern drug design[8]. Hyperphosphorylation and glycosylation might induce impairment of the protein interaction machinery. As protein expression deficiencies of SNARE members have been demonstrated in the brain at the Lewy body variant of AD patients[9], there might exist forms of T2DM in which pancreatic β-cells undergo similar expression deficiencies, but this is still a matter of investigation.

In contrast to neuronal transmitters, insulin does not undergo a reuptake into β-cells. The premature insulin granules[10] have to be transported to the cell periphery along microtubules *via* an energy-consuming process using kinesin[11]. In this respect, microtubular dynamics as well as microtubule-associated protein tau (MAPT), also named tau, play an important role. Abnormalities in tau protein structure such as tangles and hyperphosphorylated tau aggregates were identified in the brains of AD patients[12,13] about 30 years ago. This has led to the technical term tauopathy and has been defined as detergent insoluble tau aggregates forming tangels and neuritic plaques[14]. Very recently, hyperphosphorylated tau, representing a factor responsible for the inhibition of microtubule assembly and microtubule disruption[15], has been identified in pancreatic islets of Langerhans of T2DM patients[16]. In contrast, this was not found in pancreatic islets of healthy individuals. Such data have been confirmed by in vitro studies using insulinoma tissue and cell lines from rodents[17]. At least six individual tau isoforms have been identified in these rodent β-cell lines, of which two are of higher molecular weight than the brain derived isoforms. Insoluble aggregates were isolated and demonstrated. Most interestingly, a slight but not significant up-regulation of tau[18] expression could be defined at the gene level using expression screens when comparing normal age matched donor islets with pancreatic islets from T2DM patients.

Although tau has become an important molecule in defining AD pathology, it is not solely responsible for disease development[19]. In the brain, extracellular beta amyloid deposits are the second main hallmark of AD pathology. Interestingly, a homologous protein[20] named islet amyloid polypeptide (IAPP)[21] is present in beta cells, which is intriguing in this respect. It is co-expressed and secreted with insulin by pancreatic beta cells[22,23]. The IAPP has a propensity to misfold and aggregate into cytotoxic oligomers, which result in islet amyloid deposits found in T2DM patients[24]. Oligomers of human IAPP are known to cause membrane disruption[25], and are therefore involved in the mediation of β-cell apoptosis in T2DM. Interestingly, the single amino acid mutation (proline substitution) in rodent IAPP hinders the formation of IAPP deposits[22], and rodents do not spontaneously develop diabetes characterized by islet amyloid deposits[26]. This, in turn, has led to the development of transgenic rats expressing the human variant of IAPP[27]. The transgenic rat model indeed resembles the T2DM of humans closely, and provides proof that this molecule is involved in derangement of β-cell function. It is of note that, using these models, it has been shown that the toxic effect of human IAPP on β-cell apoptosis is initiated by a threshold-dependent effect[26].

MODIFICATIONS OF INSULIN SECRETION

Insulin secretion from pancreatic beta cells has been monitored in a pulsatile mode under physiological conditions[28,29]. The frequency of pulses changes depending on the blood glucose level, and can be influenced by drugs such as sulfonylurea[29]. Most interestingly, impairment of this mode of secretion has been observed much earlier than the abnormal glucose tolerance could be measured[30]. Each pulse of insulin release is preceded by an increase of intracellular calcium[29]. This tightly controlled mechanism as reviewed by Tengholm and Gylfe[31] is deranged in individuals with impaired glucose tolerance and diabetes[32,33]. Additionally, an age-dependent change in pulsatile insulin secretion has been demonstrated in animal models[34] as well as in humans[35].

β-CELL REPLICATION AND AGE

It has been demonstrated in rodent models that the beta cell mass is the result of a balanced mode of replication and apoptosis[36,37]. An adjusted increase in replication has been found in obesity of rodents[38] and humans[39]. Moreover, the adaptive increase in beta cell mass has been shown to have important biological relevance for the increased insulin demand in pregnancy[40,41,42]. Furthermore, as depicted in rats, these adaptations are necessary to balance the age-related insulin resistance building up within 12 mo of birth[34]. Data beyond this age are not available from rats, though it has to be speculated that this β-cell replicative potential decreases in rodents in an age-dependent manner[43] as it has been shown for humans[44]. In younger individuals, β-cell mass can adapt to increase in body mass in order to maintain glucose tolerance within the normal range, this seems not to be the case in older individuals.

β-CELL APOPTOSIS AND AGE

Although T2DM has been associated with increased β-cell apoptosis[44,45,46], it does not necessarily mean that there is an increase in apoptosis going along with the age. However, there exists clear evidence that islet amyloid polypeptide increases with age at the islet of Langerhans[47,48]. This physiological peptide can cause apoptosis in its oligomeric form[25,45,49,50]. In addition to this, hyperphosphorylated tau protein can accumulate within the islet of Langerhans, as mentioned above[16]. Rodent models suggest that increased apoptosis might be responsible for the decrease in β-cell mass[26,27,51,52].

PROTECTIVE EFFECTS

It has been suggested that several protective effects exist to prevent neuronal death[53,54]. The former author describes that the calcium-binding protein secretagogin might exhibit a neuro-protective effect. This protein is highly expressed at the pancreatic islet of Langerhans, and might indeed exert important sensing capabilities at the calcium spikes preceding each pulse of insulin secretion[55]. Some preliminary data have been suggested in recent work, which might indicate that this protein provides more resistance to β-cell stressors under *in vitro* conditions[17]. Similarly, chaperon proteins have been implicated in refolding proteins back into their normal structure, following derangement from their native structure due to exposure to toxins or disease-mediated changes in body temperature[56,57].

Further basic research work will be necessary to teach us how age-related changes in β-cells can be reduced, prevented and counteracted.

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